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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/918,186	07/30/2001	C. Frank Bennett	ISPH-0585	6392

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LICATLA & TYRRELL P.C.
66 E. MAIN STREET
MARLTON, NJ 08053

EXAMINER	
MCGARRY, SEAN	
ART UNIT	PAPER NUMBER
1635	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/918,186	Applicant(s) BENNETT ET AL.	
	Examiner Sean McGarry	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-15 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-15 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION **FILE COPY**

DETAILED ACTION

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 and 6-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 14-23 of U.S. Patent No. 6,335,194. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of antisense oligonucleotides used in the methods of 6,335,194 is embraced within the scope of antisense oligonucleotides contemplated in the instant invention, and the scope of venue, *in vitro*, for 6,335,194, is embraced by the broader scope of the instant application which methods embrace both *in vitro* and *in vivo*. The intersection of the scopes of the instant claims and those of 6,335,194 renders them [the claims of both applications] obvious over each other, for example.

Claims 7 and 8 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 2 of U.S. Patent No. 6,165,788. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the instant claims embraces the scope of the claims of 6,165,788, for example. The methods of the instant claims can be *in vitro* or *in vivo* and the methods of the 6,165,788 is limited to *in vitro*. The intersection of the scopes of the instant invenbtions renders them obvious over each other, for example.

Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over over Altieri et al. [WO 98/22589] in view of Baracchini et al [US 5,801,154].

The instant invention is drawn to a method of modulating apoptosis in acell via antisense oligonucleotides of 8-30 nucleotides that inhibit the expression of human Survivin..

Altieri et al have taught human Survivin and its implications in apoptosis. It has been taught by Altieri et al that there was known a natural antisense transcript against human Survivin and that expression of this transcript results in inhibition of Survivin and results in massive apoptosis and decreased cell growth (see pages 3 and 41-42, for example). It has been taught that the use of antisense oligonucleotides was expressly contemplated (see page 5, for example). At page 13 it was taught that expression of Survivin antisense inhibits cell growth.

Altieri et al do not specifically teach antisense oligonucleotides that are 8-30 nucleotide in length.

Baracchini et al have taught, at column6 for example, that antisense oligonucleotides can be used for research purposes and have also taught at column 6 that antisense oligonucleotides can be modified in their sugars, backbone linkages and nucleobases and that such modifications are desirable in antisense since these modifications have desirable properties such as, for example, enhanced cellular uptake,

enhanced affinity for nucleic acid targets and increases stability in the presence of nucleases. Baracchini et al provide specific examples of such modifications at columns 6-8 and in Example 1, for example. These specific examples taught by Baracchini et al include phosphorothioate linkages, 2'-O-methoxyethyl sugars, 5-methylcytosine and chimeric oligonucleotides, for example. Tables 1-4 show the successful design and use of modified oligonucleotides in cells in culture, for example. Table I therefore reflects the successful practice of general antisense design taught at columns 8-10, for example. At column 4 it has been taught various carriers for antisense delivery. It has been taught at column 8 that antisense are preferably 8 to 30 nucleotides and that it is more preferable to make antisense oligonucleotides that are 12 to 25 nucleotides in length, for example.

It would have been obvious to use antisense oligonucleotides 8-30 nucleotides in length to modulate apoptosis in cells since Altieri et al have taught that it would be desirable and specifically contemplate using oligonucleotides to inhibit Survivin and Baracchini et al have taught that such a size for antisense oligonucleotides is desirable, for example. One would have a reasonable expectation of success since Altieri et al expressly contemplate the use of such oligonucleotides and since Baracchini et al have taught the successful use of oligonucleotide of such length in cells, for example.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claims 1-15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for in vitro methods, does not reasonably provide

enablement for in vivo/therapeutic applications. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant invention is drawn to the treatment and in vivo application of antisense oligonucleotides for modulation of various biological systems (cell cycle, cell proliferation, apoptosis, cytokinesis,, for example) via the inhibition of Survivin in a whole animal.

The instant specification, as filed provides guidance for the inhibition of Survivin in cell in culture. Example 25 shows that skin grafts in immunodeficient mice treated with SEQ ID NO: 250 showed a reduction of Survivin protein as per immunostimulatory assay. The Example does not show the level of Survivin reduction or if the reduction was statistically significant, for example. It is not clear from this example how such an observation correlates to the treatment of various disease states with Survivin targeted antisense.

The art of nucleic acid based therapy is an unpredictable art. Branch [TIBS Vol. 23, February 1998] addresses the unpredictability and the problems faced in the antisense art with the following statements: "[a]ntisense molecules and ribozymes capture the imagination with their promise or rational drug design and exquisite specificity. [h]owever, they are far more difficult to produce than was originally anticipated, and their ability to eliminate the function of a single gene has never been proven."; "[t]o minimize unwanted non-antisense effects, investigators are searching for antisense compounds and ribozymes whose targets sites are particularly vulnerable to

attack. [t]his is a challenging quest."; "[h]owever, their unpredictability confounds research applications of nucleic acid reagents."; "[n]on-antisense effects are not the only impediments to rational antisense drug design. [t]he internal structures of target RNAs and their associations with cellular proteins create physical barriers, which render most potential binding sites inaccessible to antisense molecules."; "Years of investigation can be required to figure out what an 'antisense' molecule is actually doing,. . ."; "Because knowledge of their underlying mechanism is typically acting, non-antisense effects muddy the waters."; "because biologically active compounds generally have a variety of effects, dose-response curves are always needed to establish a compounds primary pharmacological identity. [a]ntisense compounds are no exception. [a]s is true of all pharmaceuticals, the value of a potential antisense drug can only be judged after its intended clinical use is known, and quantitative information about its dose-response curve and therapeutic index is known."; [c]ompared to the dose response curves of conventional drugs, which typically span two to three orders of magnitude, those of antisense drugs, extend only across a narrow concentration range."; "[b]ecause it is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be determined empirically by screening large number of candidates for their ability to act inside cells."; "[b]inding is the rare exception rather than the rule, and antisense molecules are excluded from most complementary sites. [s]ince accessibility cannot be predicted, rational design of antisense molecules is not possible."; and, "[t]he relationship between accessibility to ODN binding and vulnerability to ODN-mediated antisense inhibition *in vivo* is beginning to be explored. . .

[i]t is not yet clear whether *in vitro* screening techniques. . . will identify ODNs that are effective *in vivo*."

Jen et al [STEM CELLS Vol. 18:307-319, 2000] Discuss antisense based therapy and the challenges that remain before the use of antisense becomes routine in a therapeutic setting. Jen et al discuss the advances made in the art but also indicate that progress needs to be made in the art. In the conclusion of their review Jen et al assert "[g]iven the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has remained elusive." It is also stated "[t]he key challenges to this field have been outlined above. [I]t is clear that they will have to be solved if this approach to specific antitumor therapy is to become a useful treatment approach. [a] large number of diverse and talented groups are working on this problem, and we can all hope that their efforts will help lead to establishment of this promising form of therapy." It is clear from Jen et al that the state of the art of antisense is unpredictable and those highly skilled in the art are working towards making the art of antisense therapy more predictable but have many obstacles to overcome.

The instant specification does not provide one in the art with guidance such that the obstacle exemplified above have been overcome such that one in the art could predicively treat the broad range of diseases instantly contemplated. The quantity of experimentation would include determining treatment regimes de nov and further to overcome the general problems of nucleic acid therapy de novo as they apply to the specific regimens, for example.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R McGarry whose telephone number is (703) 305-7028. The examiner can normally be reached on M-Th (6:00-5:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

SRM
September 26, 2002

SEAN McGARRY
PRIMARY EXAMINER
1635